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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/652,493	BISSELL ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 22-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

In view of the Appeal Brief filed on 12 February 2004, PROSECUTION IS HEREBY REOPENED. A rebuttal to the Appeal Brief and the new grounds of rejection are set forth below.

To avoid abandonment of the application, applicant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claim 1-8, and 22-30 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The Following is a rebuttal to the Appeal Brief

Claim Rejections - 35 USC § 112

Claims1-8, and 22-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. The claims are enabled.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention of instant claims 1-4, and 22-30 is a method of detecting molecular weight of 120-130kD or 60 kD fragment of α-dystroglycan in blood and/or serum (a preferred embodiment of "a sample of medium surrounding cells"), and then correlating said detection to "potential tumorigenicity", or "tumor growth". The nature of the invention of instant claims 5-8 is a method of measuring potential tumorigenicity of cells by detecting presence of α-dystroglycan, and then correlating absence of α-dystroglycan on cell surface, more specially relative decrease of α-dystroglycan as compared to β-dystroglycan indicates a higher potential tumorigenicity.

The level of skill in the art in cancer diagnosis using a newly discovered biomarker such as α-dystroglycan in blood or serum is low and cancer diagnosis art is unpredictable. The breath of the claims are broad including any cancer. There are no working examples of detecting molecular weight of 120-130kD or 60 kD fragment of α-

dystroglycan in blood and/or serum (a preferred embodiment of "a sample of medium surrounding cells", and then correlating said detection to "potential tumorigenicity", or "tumor growth". There is also no working example of a method of measuring potential tumorigenicity of cells by detecting presence of α-dystroglycan, and then correlating absence of α-dystroglycan on cell surface, more specially relative decrease of α-dystroglycan as compared to β-dystroglycan indicates a higher potential tumorigenicity.

The amount of direction or guidance by the inventor how to use the full scope of the claimed invention is limited. The quantity of experimentation needed to use the claimed invention is large. In order to use the full scope of the claimed invention, one skilled in the art has to screen a large quantity of clinical samples to determine whether detecting molecular weight of 120-130kD or 60 kD fragment of α-dystroglycan in blood and/or serum, is correlated with a higher tumorigenicity, and one has to determine whether not detecting presence of α-dystroglycan, more specially relative decrease of α-dystroglycan as compared to β-dystroglycan indicates a higher potential tumorigenicity.

At page 6 of the Appeal Brief, applicant argues that the method may not be a fully developed method immediately suitable for clinical use, but it has sufficient utility to meet the requirements of 35 USC 101. The prosecution history indicates that the claimed invention is not rejected under 35 USC 101; therefore this is a moot issue.

Applicant at page 6 also argues the examiner doubts the assertion made throughout the specification by the inventors, both Ph.D. scientists doing full time research in this field. The examiner acknowledges that the inventors are highly regarded scientists as the attached CV indicates. The enablement rejection is not

based on lack of the inventors' credentials, but based on whether undue experimentation is necessary in order to practice the invention.

Applicant at page 6 cites MPEP 2164.04 for that there is no basis to doubt applicant's assertion, therefore claims are enabled. However, cancer diagnosis or prognosis is unpredictable as shown by Wirth et al., of record (Eur Urol 1993;24 Suppl 2:6-12, Abstract only) and Tockman et al of record (Cancer Res., 1992, 52:2711s-2718s). Wirth et al (Eur Urol 1993;24 Suppl 2:6-12, Abstract only) teach that the well-known blood circulating prostate tumor maker (i.e. PSA) by shedding of prostate membrane antigen is detected in normal blood. PSA concentration in blood is relevant as cancer marker, not just presence or absence of it. The specification does not provide a single in vivo control value. As stated in the previous Office actions, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to instant invention. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of tumorigenicity have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed)

cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). The specification does not teach if the proteolytic fragment could be used as a biomarker for potential tumorigenicity detected in blood or any other in vivo medium surrounding the cells. In other words, the specification does not teach an in vivo control value as compared to an in vivo cancer sample value.

Applicant's argues that there may be cases where normal cells shed α-dystroglycan is a pure speculation. However, the specification does not have any experimental evidence to back up applicant assertion. Matsumura et al., of record (cited in the Office action mailed on 4/23/2002, J. Biol. Chem. 272, pages 13904-10) in the last sentence of the paragraph bridging page 9-10 clearly states a research is needed to determine whether secretion of α-dystroglycan in vivo occurs for some regulatory reasons. The specification does not teach a single in vivo control sample as related to the instantly claimed invention. The specification does not teach that α-dystroglycan fragments of 120-130 kD or the 60 kD normal in vivo model animal is not

detected whiled said fragments are detected in blood and/or serum in vivo model afflicted with a tumor. Applicant's argument that the inventors of the instant application are so well regarded in the field, therefore their assertions alone without in vivo experimental data should be accepted as enabling disclosure is not persuasive.

The invention of claims 5-8, drawn to a method of measuring potential tumorigenicity of cells by detecting presence of α-dystroglycan, then correlating absence of α-dystroglycan on cell surface, more specially relative decrease of α-dystroglycan as compared to β-dystroglycan indicates a higher potential tumorigenicity.

The specification does not teach any in vivo example of detecting absence of α-dystroglycan on cell surface or detecting relative decrease of α-dystroglycan on cell surface as compared to β-dystroglycan in any in vivo cancer samples.

Rather, the specification discloses:

1) At Fig. 1, and Examples 1 and 2 (pages 17-20), a smaller fragment (120-130 kDa) of alpha-dystroglycan is detected in the supernatant of SCg6 mammary carcinoma cell line culture and this detection is due to shedding of proteolytic fragment of 180 kDa alpha-dystroglycan (normal size) , adding a metaloprotease inhibitor GM6001 to the cell culture reduces this shedding.
2) At Fig. 2, the immunoblot of whole cell extracts show that some cell lines express both alpha- and beta dystroglycan for example BT474, lane 2, and other cell lines express only beta-dystroglycan for example, MCF-7.

3) At Fig. 3, and Example 3 (page 20-23), adding the metalprotease inhibitor restores the tumor phenotype of several tumor cell lines.

4) At Example 5 (pages 24 and 25) restoration of dystroglycan function to the tumorigenic cell line HMT-3522-T4 by transfection of DNA overexpressing a human dystroglycan restored normal phenotype of the cell line, or nude mice injected with cancer cells with restored dystroglycan function do not develop cancers but mice with the control develop cancer.

However, Henry et al., newly cited in this Office action (2001, Human Pathology, vol. 32, pages 791-795) teach that in case of in vivo prostate and breast tumors, β-dystroglycan detection on cell surface is reduced. Note the authors of the study used antibody specific for β-dystroglycan. Henry et al., teach at the last paragraph of page 792, left column that tumor cells with a higher tumorigenicity has undetectable β-dystroglycan on the tumor cell surfaces. Note the statement "In 15 cases of prostate adenocarcinoma, DG [β-dystroglycan] was undetectable in the small, irregular pseudoglandular elements that typify mid-to high grade disease (Fig. 2B, D)." Thus, Henry et al., teach decreased amount of β-dystroglycan is correlated with a higher tumorigenicity. Thus, one skilled in art would be required to resort to undue experimentation to resolve the differences shown in in vivo cancers data by Henry et al., and applicant's assertion based on in vitro data that absence of α-dystroglycan on cell surface (due to shedding of said α-dystroglycan based on cell culture medium data) or detecting relative decreased amount of α-dystroglycan on cell surface as compared to β-dystroglycan is indicative of higher potential tumorigenicity.

B. The Declaration of Dr. Judith Campisi provides objective evidence that the claims are enabled.

Both Applicant and the Office agree that Dr. Judith Campisi is a highly regarded scientist. However, the declaration by Dr. Judith Campisi is an expert opinion. The declaration does not provide objective evidence as regard to the claimed invention is enabled. The declaration does not provide any objective evidence that the claimed invention is enabled i.e. there is no data in the declaration to support that detecting molecular weight of 120-130kD or 60 kD fragment of α-dystroglycan in blood and/or serum (a preferred embodiment of "a sample of medium surrounding cells") is correlated with potential tumorigenicity, and/or absence of α-dystroglycan on cell surface or detecting relative decrease amount of α-dystroglycan on cell surface as compared to β-dystroglycan is correlated with a higher potential tumorigenicity,.

Dr. Campisi states in Paragraph 5 of the declaration that in her opinion, a number of in vitro cell culture models are generally recognized in the art as correlating to in vivo conditions of tumorigenicity potential, the three dimensional basement membrane assay, nude mice in vivo experiment, are presented in the specification, and nude mouse model is generally accepted as a model predictive of human tumor cell behavior. Thus, extrapolating the detection of the dystroglycan fragments found in cell culture medium to the ability to find that same fragments using similar techniques in the blood or other tissue of a living animal. Based on her review of the specification at page 11, first paragraph, also the page 13-14, Dr. Campisi concludes that in her opinion that the

weight of scientific evidence favors the statement of the specification quoted in Paragraph 6.

The specification at Fig. 3 and pages 10, 11, and 24-25 teaches that restoring α-dystroglycan function by transfecting DNA encoding α-dystroglycan protein converts tumorigenic behavior of cells in a 3D base membrane assay, and tumor cells over-expressing α-dystroglycan do not cause tumor growth in nude mouse. These data in the specification that Dr. Campisi refers to are enabled for method of suppressing tumorigenic potential of cells or animal but the claimed invention is not enabled for claimed invention, drawn to method of detecting molecular weight of 120-130kD or 60 kD fragment of α-dystroglycan in blood and/or serum (a preferred embodiment of "a sample of medium surrounding cells"), and then correlating said detection to "potential tumorigenicity", or "tumor growth". This enablement rejection is not about raising doubts about the truth of the statement at page 11 or page 13-14 as suggested in the Paragraph 7 of Dr. Campisi's declaration. Rather, it is about whether one of skill would have to resort to undue experimentation in order to practice the claimed invention. The art recognizes cancer diagnosis using a newly discovered marker is not a trivial matter. It is not clear whether the 120-130 kD or the 60 kD fragment is circulating in the blood or the fragments are further degraded into smaller fragments by many proteolytic enzymes present in vivo such that 120-130 kD or the 60 kD fragment is not present in blood and/or serum of in vivo subject. Further, it is not clear whether the antibody disclosed in the instant application could be used to detect the fragment(s) circulating in blood if the fragments are further degraded. Applicant posses the necessary reagents and in vivo

mice model for determination of whether or not the claimed 120-130 kD or 60 kD fragment is circulating in the blood. Data collected by an undergraduate student are given more weight in terms of enablement analysis than an expert's opinion.

The Office does not have a facility to determine whether the blood sample obtained from the nude mice received α-dystroglycan function restoring cells do not contain 120-130 kD or 60 kD fragment but the blood samples from the nude mice exhibiting malignant phenotype contain 120-130 kD or 60 kD fragment. Further, it is not clear whether presence of the fragments could be applicable to all types of cancers or specific types of cancer. It is not clear whether the fragments could be detected in sputum, saliva, all other possible medium surrounding "a medium containing cell" in vivo. In order to answer these kinds of questions, one of skill has to screen a number of large clinical samples. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use the alleged discovery, not how to screen it for themselves.

C. Clinical trials or other in vivo data are not required under 35 USC 112 and are necessary to show a reasonable expectation of success in this case.

Applicant states "how to use" prong utility requirement does not require in vivo data for a biological invention and cites MPEP 2164.02, then concludes that the invitation in the Final Office action that applicant supply vivo data is improper. This argument has been fully considered but found unpersuasive because the disclosure in the specification and the claimed invention do not correlate well.

As the disclosure in the specification as summarized in the Office action on 11/06/2002 at page 3 indicates, only detection of α-dystroglycan fragments recited in instant claims is in medium of cells have been maintained in vitro. The art recognizes that cells maintained in vitro have different characteristics than in vivo cells. Freshney of record (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer of record (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years.

Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that the proteolytic fragments could be detected in blood *in vivo*. The *in vitro* demonstration of restoring normal phenotype of cancer cells with the protease inhibitor or with overexpression of human dystroglycan cannot be correlated to the invention as claimed, because the characteristics of cultured cell lines generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers.

In vivo data to obviate this rejection do not necessarily involve human clinical trials. Data obtained from using in vivo animal model including a control would be sufficient for enablement determination under 35 USC § 112, first paragraph. The Office does not require applicant to submit data for efficacy in human clinical trials. Here, the Office emphasizes again that in vivo data does not necessarily means human clinical data, but in vivo data that is relevant to the claimed invention collected from in vivo animal model would be sufficient for enablement determination under 35 USC § 112, first paragraph. In other words, in vivo data collected by a summer undergraduate student intern would be sufficient; obtaining blood samples from mice who have a higher tumorigenic potential, running SDS PAGE, followed by immunoblot as shown in Fig. 2 for example, and then comparing the immunoblot with that of control sample would be sufficient for enablement analysis under 35 USC § 112, first paragraph. Applicant has not provided any objective in vivo animal model data given

the art recognizes that in vivo environment is much more complicated than the in vitro cell medium that in vitro cells face.

Applicant concludes at page 9 that the case involves a novel finding in the relationship between the cell membrane and the extracellular matrix, modeling of in vivo cell behavior in an in vitro extracellular matrix model is accepted in the art. These assays applicant referring to is an accepted model for method of restoring α-dystroglycan function, not by detecting 120-130 kD or the 60 kD fragment of α-dystroglycan in blood, then correlating the detection to higher tumorigenic potential of cell in vivo. Applicant is not claiming method of reducing tumorigenic potential using the tumor suppressor, α-dystroglycan. A method of reducing tumorigenic potential using the tumor suppressor, α-dystroglycan is enabled but the claimed method is not enabled.

One cannot extrapolate the teachings of the specification to the claimed invention because the specification provides neither guidance on nor exemplification of how to correlate the data presented in the specification with the ability to detection of α-dystroglycan fragments in blood and/or serum for the assessment of cancer risk. It is not clear whether the 120-130 kD or the 60 kD fragment is circulating in blood in vivo or the fragment is further degraded into smaller fragments by many proteolytic enzymes present in vivo. The specification does not teach if some normal cells in vivo secrete the fragments for yet unknown functions. In summary, the specification does not disclose any control value. The specification does not teach if one can determine tumorigenic potential of all cancers including skin, lung, or breast cancer by detecting 120-130 kD or the 60 kD fragment of α-dystroglycan in blood. If a120-130 kD or the 60

kD fragment of α-dystroglycan is detected from the blood sample of a subject for example, a mouse or guinea pig, what does it not mean? Doe that subject have a higher tumorigenic potential to develop leukemia, or breast cancer, or something else? How about a strong signal in an immunoblot vs. a weak signal? When one would expect false positive vs. false negative? What is the normal control value?

Further, the entire specification is about loss of α-dystroglycan function due to shedding is associated with higher tumor potential. However, Henry et al (cited above) teach that in vivo tumors with a higher tumorigenic potential have lower expression of β-dystroglycan, thus, suggesting loss of β-dystroglycan is correlated with a higher tumorigenic potential in vivo.

Considering lack of examples and the limited teachings of the specification, and unpredictability of art in measuring tumorigenic potential, the nature of the invention, the broad scope of the claims, the quantity of experiments required, it is concluded that undue experimentation would be required to practice the claimed invention.

The Following is a New Ground of Rejection

Claim Rejections - 35 USC § 112

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is confusing because it depends on the base claim 5. Claim 5 does not say anything about measuring β-dystroglycan and conclusion step of claim 5 is limited to absence of α-dystroglycan on cell surface. It is not clear how claim 8 is related to the

base claim. It appears that the conclusion step of base claim 5 and the conclusion step of claim 8 are in conflict of each other. In summary, how is "absence" in line of claim 5 is related to "relative decrease" in line 3 of claim 8 related? It appears that claim 8 is broadening scope of the base claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina C Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
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